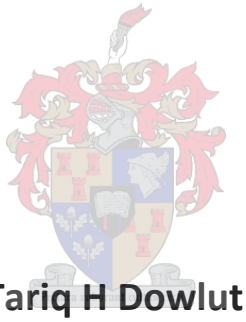
ENDOMETRIAL CANCER IN YOUNG WOMEN

A Retrospective Matched Cohort Study



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Declaration

By submitting this thesis electronically, I declare that the entirety of the work contained therein is my own, original work, that I am the sole author thereof (save to the extent explicitly otherwise stated), that reproduction and publication thereof by Stellenbosch University will not infringe any third party rights and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

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ABSTRACT

OBJECTIVE: Endometrial cancer is the second most common gynaecological cancer in South Africa. It typically arises in the sixth and seventh decades of life. However, an increasing number of premenopausal women are being diagnosed with endometrial cancer. Delay in diagnosis in younger women is due to symptoms being ascribed to abnormal uterine bleeding. The objective of this study was to carry a review of the clinical, pathological and management of endometrial cancers in younger women to identify risk factors, characterise histology and appraisal of treatment received.

METHODS: We did a retrospective matched study of a cohort of women aged 55 years or younger with histologically confirmed endometrial carcinoma. Each case was matched to two randomly selected control cases of histologically proven endometrial cancer patients aged more than 55 years old. It was conducted at Tygerberg Hospital, the largest tertiary hospital in the Western Cape Province of South Africa. We examined patient folders from the Department of Gynaecologic Oncology from 2014 – 2018. Clinical characteristics including age, parity, hypertension, diabetes mellitus, hormone therapy, tamoxifen use, personal history of cancer and family history of cancer were obtained. Outcomes including histological type and grade, myometrial depth invasion, lympho-vascular space invasion, lymph node involvement, extrauterine spread, stage, treatment plan and need for adjuvant therapy were reviewed.

RESULTS: 15 patients 55 years of age or less were identified (range 40-55, median 52). Only 20% were nulliparous. All the patients had at least class 2 obesity with 50% having class 3 obesity. The incidence of hypertension and diabetes were 66.7% and 56.7% respectively. Only 2 patients had a history of tamoxifen use for breast cancer. 33.3% had a personal history of a cancer and 26.7% reported having a first degree-relative with cancer. All the 15 patients (100%) in the younger cohort had Type I (endometrioid adenocarcinoma) compared to 50% in more than 55-year-old group. Statistical significance differences were found for histological grade (p-value 0.004), myometrial depth invasion (p-value 0.02), extrauterine spread other than lymph node (p-value 0.006) and need for adjuvant therapy (p-value 0.007). No significant differences were found for lympho-vascular space invasion (p-value 0.18), lymph node spread (p-value 0.95) and stage (p-value 0.107). Despite no statistical significance was found for overall disease stage between the two groups, 11 patients (73.4%) presented with stage I disease in the younger cohort. None of the patients received conservative management and were surgically staged by open laparotomy.

CONCLUSION: Obesity is a significant risk factor in our population. Oestrogen excess seems to be the main aetiology of endometrial cancer in the local population. Younger patients typically present with Type I endometrioid adenocarcinoma, low grade and less myometrial invasion. There is less need for adjuvant radiotherapy in this group of patients.

INTRODUCTION

Endometrial carcinoma is the second most common gynaecological cancer in South Africa, cervical cancer being the most common. [1] In the United States, for 2019 it was estimated that about 61,880 new cases of endometrial carcinoma will be diagnosed and about 12,160 women will die from it. [2]

It typically arises in the sixth and seventh decades of life with a mean age of 63 years at diagnosis. [3] However, an increasing number of premenopausal women are being diagnosed with endometrial cancer. The difficulty in diagnosis in pre-menopausal is likely due to symptoms being often confused with abnormal uterine bleeding.

RISK FACTORS

Systemic unopposed oestrogen therapy results in a markedly increased risk of endometrial hyperplasia or carcinoma. Endometrial hyperplasia has been demonstrated in 20 to 50 percent of women after one year of receiving systemic oestrogen therapy without a progestin. [4] Several studies have shown an increased incidence of endometrial carcinoma, and is related to both oestrogen dose and duration of use.

Tamoxifen is a selective oestrogen receptor modulator with both agonist and antagonist properties, depending upon the individual target organ and circulating levels of serum oestrogen. It is the most widely used anticancer drug, and has been suggested by some studies to cause an increased incidence of adenocarcinoma of the endometrium. [5]

In anovulatory women, sex hormones are produced, but not cyclically, leading to irregular menstrual cycles. This results in chronic oestrogen production that is unopposed by adequate progesterone production which allows continued proliferation of the endometrium. Eventually this can lead to endometrial hyperplasia or carcinoma. Moreover, other endocrine disorders associated with anovulation such as polycystic ovary syndrome (PCOS), thyroid disorders, and elevated prolactin level are risk factors for the endometrial carcinoma. [6] [7] [8]

Early menarche and late menopause are factors that result in prolonged oestrogen stimulation and at times of reproductive years during which anovulatory cycles are common. [9]

Nulliparity and infertility are risk factors for endometrial carcinoma which are likely associated with the high frequency of anovulatory cycles in those women. It was found that the risk of endometrial carcinoma is inversely related to parity. [10]

Obesity is strongly associated with endometrial cancer with the level of risk related to the degree of obesity. [11] This may be due to the high levels of endogenous oestrogens from the conversion of androstenedione to oestrone and the aromatization of androgens to oestradiol, both of which occurs in peripheral adipose tissue in obese women. Additionally, obese women have lower circulating levels of sex hormone binding globulins leading to increased steroid hormone activity. [12]

Women with diabetes mellitus and hypertension are at increased risk for endometrial carcinoma. Comorbid factors, primarily obesity, account for much of this risk even though some studies have shown them to be independent risk factors. The risk of developing endometrial carcinoma is higher in type 2 than type 1 diabetics. [13]

Lynch syndrome is an autosomal dominant disorder that is caused by a germline mutation in one of several DNA mismatch repair genes. Women with Lynch syndrome are at higher risk of developing endometrial carcinoma especially at a young age. [14]

Family history for endometrial carcinoma alone has been suggested for first-degree relatives, but no candidate genes have been identified consistently. [15]

In South Africa as well as most of the rest of the world, obesity has reached epidemic proportions. This is mainly due to a progression towards industrialized societies whereby fast foods are readily available and cheap. Together with the lack of exercise due to the constraints of the corporate world of today, obesity is slowly and increasingly becoming the norm. This has led to a rise of young women affected with metabolic syndrome. Both obesity and metabolic syndrome have been shown to be independent risk factors for endometrial carcinoma.

Nowadays contraception is strongly encouraged, and several campaigns are aimed at improving the socio-economic status of women. Moreover, an increasing number of perimenopausal women are seeking hormone replacement therapy to improve their quality of life by limiting, often distressing, symptoms

such as hot flushes, mood lability and vaginal dryness, and to protect them from conditions such as osteoporosis and ischemic heart disease. It is well known that unopposed oestrogen therapy leads to endometrial hyperplasia and at a high risk of progression to endometrial cancer.

There has been a gradual decline in the average age of menarche over the last century. Currently the average age at menarche in the United States is about 12.5 years. [16] Anovulatory cycles with an unopposed oestrogen stimulated endometrium around menarche is quite common. As stated above early menarche has been associated with an increased risk of developing endometrial carcinoma.

With improved access to education and better opportunities for work, nowadays women are having less children. With the inverse correlation of parity with endometrial cancer, we should expect a rise in the number of cases.

With an expected rise in endometrial carcinoma in premenopausal women, along with its diagnostic challenges and unique management strategy pertaining to fertility preservation in some cases, it is important to properly investigate how to address the risk factors and assess the best management options in a South African setting.

PATHOLOGY

Endometrial carcinomas are classified into two major types I and II. [17] Type I tumours include tumours of endometrioid histology that are grade 1 or 2. These comprise approximately 80 percent of endometrial carcinomas. These tumours are oestrogen responsive and typically have a good prognosis. They are associated with obesity, nulliparity, insulin resistance and hyperoestrogenism. At a molecular level, mutations in the PTEN tumour suppressor gene, k-ras oncogene and mismatch repair genes are often found. [18] They also commonly stain positively for oestrogen and progesterone receptors.

Type II tumours account for 10 to 20 percent of endometrial carcinomas. These tumours are oestrogen independent, are often high grade and have a poor prognosis. They include grade 3 endometrioid tumours as well as tumours of non-endometrioid histology: serous, clear cell, mucinous, squamous, transitional cell, mesonephric, and undifferentiated. These tumours are not associated with the risk factors of Type 1

cancers and typically occur in older women. They are associated with mutations of the p53 tumour suppressor gene. [17] [18]

Macroscopically, endometrial carcinomas may be visible as a single dominant mass within the endometrial cavity, may involve much of the endometrial cavity as friable neoplasm, or may be subtle or undetectable grossly as it diffusely replaces the endometrium and/or myometrium.

Histologically, endometrial carcinomas are characterized according to the World Health Organization and the International Society of Gynaecological Pathologists. Table 1 below shows the different histological subtypes of endometrial carcinomas.

Table 1

HISTOLOGIC SUBTYPES OF ENDOMETRIAL CARCINOMA
Endometrioid adenocarcinoma • Variant with squamous differentiation • Villoglandular variant • Secretory variant • Ciliated cell variant
Serous adenocarcinoma
Clear cell carcinoma
Mixed adenocarcinoma
Mucinous adenocarcinoma
Squamous cell carcinoma
Transitional cell carcinoma
Small cell carcinoma
Undifferentiated carcinoma

Tumours of the Breast and Female Genital Organs, WHO/IARC Classification of Tumours 2003

CLINICAL FEATURES

As Bokhman suggested, Type I endometrial carcinoma typically have features of obesity, particularly upper body fat distribution, hyperlipidaemia, insulin resistance, and signs of hyperoestrogenism, such as anovulatory uterine bleeding, infertility, late menopause and hyperplasia of the stroma of the ovaries and endometrium. Type II endometrial carcinoma have less clearly defined features. [17] Ninety percent of patients with endometrial carcinoma present with abnormal uterine bleeding.

Thus, a high degree of suspicion for endometrial carcinoma must be exercised in patients with the following presentations:

- All patients with postmenopausal bleeding
- Postmenopausal women with a haematometra or pyometra
- Asymptomatic postmenopausal women with endometrial cells of Papanicolaou smear, particularly if they are atypical
- Perimenopausal women with intermenstrual bleeding or progressively heavy menstrual bleeding
- Premenopausal women with abnormal uterine bleeding, particularly if there is a history of anovulation

MANAGEMENT

Traditionally the definitive treatment of endometrial cancer, regardless of the age of the patient or stage of the tumour, consists of hysterectomy and bilateral salpingo-oophorectomy, with pelvic and paraaortic lymphadenectomy if indicated.

However, in young premenopausal women with endometrial cancer this standard treatment may seriously affect their quality of life due to loss of fertility and ovarian function.

According to the CDC, the proportions of first birth to mothers aged 25 and above has risen steadily from 2000 to 2014. [19] Hence, we expect to encounter more patients who are nulliparous and having a desire for childbearing. Therefore, it is imperative that these patients are provided with fertility preserving

options so as to allow them to become pregnant and at the same time provide adequate treatment for the cancer. Indeed, several studies have shown the feasibility and safety for conservative management of endometrial carcinoma in a select group of young premenopausal women. [20-22]

Moreover, early oophorectomy in these young women causes surgical menopause, resulting in premature climacteric symptoms such as hot flushes, night sweats, sleep disturbances, decreased libido and vaginal dryness which severely affects their quality of life at a young age. It also predisposes these patients to more serious long-term sequelae such as increased risk of cardiovascular diseases [23] , osteoporosis, hip fracture [24] and cognitive decline. [25]

However, ovarian preservation in these patients raises concerns in two important aspects. Firstly, is the possibility of coexisting ovarian cancer as either a metastasis from endometrial cancer or a synchronous primary tumour. Secondly is the concern that continued oestrogen production by the ovaries may stimulate residual endometrial cancer cells. However, several studies looking into the adverse outcomes of premenopausal patients selected for ovarian preservation have no significant impact on overall survival.

CONSERVATIVE MANAGEMENT

The key issues that must be considered when offering a conservative approach to endometrial cancer are divided in three categories:

- Assessment of the tumour's histological type, grade, myometrial invasion, lympho-vascular space invasion and presence of metastatic or synchronous ovarian carcinoma.
- Choosing the optimal type, dose, and duration of treatment
- Assessing treatment efficacy and surveillance for recurrence

Patient Selection

According to the National Comprehensive Cancer Network guidelines [26] and the ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer [27], the selection of ideal candidates for a conservative approach should include:

- Histological diagnosis of grade 1 endometrial carcinoma. Endometrial sampling should be done by dilatation and curettage as it has been shown to be superior to pipelle biopsy in terms of accuracy of the tumour grade. [28]
- The histological diagnosis must be confirmed by an expert gynaecological pathologist to improve accuracy of histological assessment and reliability of tumour grading.
- Initial stage should be confirmed by magnetic resonance imaging to exclude overt myometrial invasion and adnexal or lymph node involvement.
- Patients must be informed that fertility-sparing treatment is a non-standard treatment. The benefits and adverse outcomes must be discussed. Patients should be willing to accept close follow-up and be informed of the need for future hysterectomy.

Type, Dose and Duration of treatment

There is no consensus regarding the ideal progestin agent, dose or duration of treatment. The two most common progestins used are medroxyprogesterone acetate (MPA) and megestrol acetate (MA). ESGO recommends MPA at a dose of 400-600 mg daily or MA at a dose of 160-320 mg daily. [29] Treatment duration is recommended for at least six months. [30] Longer treatment durations can be considered in obese and anovulatory patients as they tend to be more resistant. However, evidence supporting longer treatment durations to achieve a late response is weak.

Even though response rate is significant, prolonged high dose progestin also carry risks of adverse effects such as thrombophlebitis, weight gain, headaches, sleep disorders, mood and libido changes, and leg cramps. Therefore, compliance issues must be properly addressed. In such cases a progestin-releasing intrauterine device (levonorgestrel IUD) may be considered. Most studies however did not report any serious adverse outcomes.

Surveillance for response to treatment

Most patients (72.2%) will show tumour regression with 6 months of treatment with progestins [30] , but recurrence rates are 30%-40%. [20] ESGO recommends performing D&C, hysteroscopy and imaging (for assessing endometrial thickness and excluding any adnexal masses) at 6 months to assess response. [27]

[29] In case a complete response is achieved, it is recommended to refer the patient to a fertility unit to achieve pregnancy earlier as the rate of recurrence is quite high. Until pregnancy is achieved, it is advisable to do close follow-up in terms of symptoms and pipelle biopsy every 6 months to detect any recurrence.

If the patient wishes to defer pregnancy, maintenance therapy with low-dose cyclic progestin or a progestin-containing intrauterine device is recommended. This regimen is also associated with a lower recurrence rate. [21]

It was previously thought that progesterone receptor status (PgR) might be reliably used as a surveillance tool for monitoring response to treatment and recurrence of endometrial carcinoma. Indeed, some studies found a significant correlation between presence or absence of PgR and response to progestin treatment. [31] [32] However, Duska et al showed that PgR positivity or negativity was comparable between responders and non-responders [33] and Yamazawa et al showed that all patients with complete response expressed PgRs whereas only 50% of patients with negative PgR status showed complete regression of the disease [34] . Accordingly, ESGO does not recommend routine testing for PgR status as 50% of patients who do not express PgRs will still respond to progestin therapy. [27] [29]

Finally, patients who presents with persistent disease confirmed by D&C at 6 months should be offered a hysterectomy. Partial responders at 6 months (complex atypical hyperplasia) could be offered another trial of progestin therapy for 3 to 6 months. [27] [29]

Pregnancy Outcome

Several studies have shown a favourable outcome for patients attempting pregnancy after complete remission of disease. [20] [35] [36] Moreover, pregnancy was significantly associated with an overall reduction in recurrence rate and a significant improvement in disease-free survival. [36] [37] After successful pregnancy the patient should be offered hysterectomy and salpingo-oophorectomy. Preservation of the ovaries can be considered depending on the age and genetic risk factors.

Emerging methods of conservative treatment

Hysteroscopic tumour resection of localized endometrial carcinoma followed by progestational therapy has been investigated in recent years. Results from those studies have been promising, however the studies are few and sample size small. [38-41]

Photodynamic therapy was recently introduced as a novel treatment for endometrial carcinoma. It uses a light-sensitive compound which upon expose to light of a particular wavelength generates oxygen free radicals that are causes cellular damage to the surrounding tumour. So far, only one report has been published. [42]

Definitive treatment

In patients failing to respond to therapy, either as disease progression, lack of regression, or recurrence of the tumour, definitive therapy consisting of hysterectomy and salpingo-oophorectomy should be offered. As discussed above ovarian preservation may be considered depending on the age and genetic risk factors of the patient.

SURGICAL MANAGEMENT

Preoperative work-up

A thorough family history must be taken and particular attention given to the Bethesda criteria to identify patients at risk for Lynch syndrome. All patients with endometrial cancer aged less than 60 must be undergo tumour evaluation for microsatellite instability (MSI) and immunohistochemistry for the expression of DNA mismatch repair (MMR) proteins to identify who should be referred for germline mutation testing and genetic counselling.

A detailed medical history must be sought. Indeed, endometrial cancer is frequently associated with the metabolic syndrome, which includes obesity, diabetes mellitus and hypertension. Presence of these comorbidities significantly increases the risk for surgical complications and a benefit-risk assessment must be undertaken in planning the modality and extent of surgery during operative staging.

A complete and thorough pelvic and general physical examination must be carried out. Particular attention must be given to the size and mobility of the uterus, presence of extrauterine masses, ascites, and lymphadenopathy.

Together with the pelvic examination, transvaginal ultrasonography (TVUS) is mandatory for clinical staging and assist in establishing a tentative International Federation of Gynaecology and Obstetrics FIGO staging before definitive pathology. This allows for the assessment of tumour size, ruling out any adnexal masses and the extent of myometrial and cervical stromal invasion. Other imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) can be sought as indicated, but not routinely, to rule out any ovarian, nodal, peritoneal or metastatic disease. [27] Furthermore, in clinical stage 1 grade 1 and 2, when lymph node dissection (LND) is considered, contrast-enhanced MRI has been shown to be superior in assessing myometrial and cervical stromal invasion. [43]

Serum tumour markers such as cancer antigen 125 (CA 125) and human epididymis protein 4 (HE4) have been found to have a significant correlation with FIGO stage, grade, lymph node metastases, myometrial invasion and cervical stromal involvement. [44-46] However, since cut-off values have not been established so far, their usefulness as a pre-operative risk stratification are limited.

Finally, before planning surgery, one should consider the clinical stage of the disease, grade, and histopathological type of the tumour (endometrioid versus non-endometrioid).

Surgical management of apparent stage 1 endometrial cancer.

The standard treatment of stage 1 endometrial cancer patients consists of total extra-fascial hysterectomy with bilateral salpingo-oophorectomy without vaginal cuff.

Ovarian preservation

Early oophorectomy in young premenopausal women results in surgical menopause, leading to premature climacteric symptoms such as hot flushes, night sweats, sleep disturbances, decreased libido and vaginal

dryness, which severely affects their quality of life at a very young age. It also predisposes these them to more serious long-term sequelae such as increased risk of cardiovascular diseases [23] , osteoporosis, hip fracture [24] and cognitive decline. [25]

On the other hand, ovarian preservation raises concerns in two important aspects. Firstly, is the possibility of coexisting ovarian cancer as either a metastasis from endometrial cancer or a synchronous primary tumour. Walsh et al. reported that among 102 young women (aged 24-45 years) who underwent hysterectomy for endometrial cancer, 26 (25%) were found to have coexisting epithelial ovarian tumours: 23 were classified as synchronous primaries, and 3 as metastases. Among the 26 cases of coexisting ovarian involvement, 4 (15%) had normal preoperative imaging of the adnexa, and 4 (15%) had benign-appearing ovaries at the time of intraoperative assessment. [47] In a more recent study, Lin et al. found that ovarian involvement occurred in 5% of patients with clinical stage I endometrial cancer, and microscopic ovarian involvement without grossly visible lesions only occurred in 0.8% of the patients. [48] Secondly is the concern that continued oestrogen production by the ovaries may stimulate residual endometrial cancer cells. However, four retrospective studies investigating the effects of oestrogen replacement therapy (ERT) after surgical treatment of early-stage endometrial cancer have found no significant increase of recurrences or death by endometrial cancer in the ERT group. [49-52] Moreover, a prospective randomized controlled trial of ERT by the Gynaecologic Oncology Group, reported no increased risk of recurrence or death in the ERT group compared with the placebo group and the incidence of new malignancy was low. [53]

Indeed, several studies looking into the adverse outcomes of premenopausal patients selected for ovarian preservation have had no significant impact on overall survival. [54-56] Accordingly, the current consensus is that ovarian preservation can be considered in patients younger than 45 years of age with grade 1 early endometrial cancer and with myometrial invasion of less than 50% and no obvious ovarian or other extra-uterine disease. Moreover, salpingectomy is recommended. Finally, patients with a family history of cancer have an increased risk of developing ovarian cancer such as BRCA mutation and Lynch syndrome are not candidates for ovarian preservation. [27]

Lymphadenectomy

Lymphadenectomy constitutes a key aspect of a comprehensive staging of endometrial cancer. It allows effective planning of adjuvant therapy, yields important prognostic information and has a therapeutic benefit. Tumour spread is determined by the FIGO stage and histological grade of the tumour. Moreover, histological type (non-endometrioid types such as serous or clear cell), more than 50% myometrial invasion, tumour size > 2cm also indicates a high risk of lymph node involvement. [57, 58] Indeed, Creasman et al found nodal involvement in up to 10% of women with even early-stage disease. [58]

However, in women with early stage, low grade, and favourable histological type tumours (endometrioid), the therapeutic effect of lymph node dissection (LND) is subject to controversy. Two randomized controlled trials showed no evidence of improvement in overall and recurrence-free survival in patients with early endometrial cancer undergoing pelvic lymphadenectomy compared to no lymphadenectomy. [59, 60] In addition, a recent Cochrane database systematic review found no evidence that lymphadenectomy decreases risk of death or disease recurrence compared with no lymphadenectomy in women with presumed stage I disease. [61] Furthermore, the authors reported no difference in direct surgical morbidity between the two groups but the incidence of surgery-related systemic morbidity such as lymphedema and lymphocyst formation was significantly higher in women who underwent lymphadenectomy. [61]

The present consensus is that lymphadenectomy is not recommended for patients with low-risk endometrioid carcinoma (grade1 or 2 and superficial myometrial invasion <50%). [27] For patients with intermediate risk (deep myometrial invasion >50% or grade 3 with superficial myometrial invasion <50%) the present data showed no survival benefit, and lymphadenectomy can be considered for staging purposes only. In addition, for high-risk patients (grade 3 with deep myometrial invasion >50%), lymphadenectomy is indicated.

Sentinel node sampling

Lymph node sampling in all women with endometrial cancer has been recommended by some experts. Clinically suspicious nodes found during surgery must be sampled and if no suspicious nodes are found, a representative pelvic and para-aortic lymph node sample must be excised. This has the benefit of

providing information about lymph node status and subsequent adjuvant therapy if indicated while minimizing adverse surgical outcomes such as lymphedema and lymphocyst formation.

Recently *sentinel lymph node mapping and dissection (SLND)* has been explored as a possible alternative to lymphadenectomy. The concluded FIRES trial found that SLND has a high accuracy for detecting endometrial cancer metastases and can safely replace lymphadenectomy in staging. It did not however identify 3% of positive lymph node patients. [62]

STUDY METHODOLOGY

Objectives

The aim of this study is to:

- Identify significant risk factors for EC in young women
- Characterize the histologic type, grade and stage, and the treatment offered in that select group of patients
- The analysed data will be compared with available literature and identify areas where standard of care can be improved

Study design

This is a descriptive, retrospective, matched study of a cohort of women aged 55 years or less with histologically confirmed endometrial carcinoma. Each case was matched to two randomly selected control cases of histologically proven endometrial cancer patients aged more than 55 years old.

Setting

The study was conducted at Tygerberg Hospital, department of Obstetrics and Gynaecology, division of gynaecologic oncology. Tygerberg Hospital is one of two public tertiary academic hospital managing cancer patients in the Western Cape Province of South Africa.

Inclusion and exclusion criteria

All women, aged 55 or less, with histologically proven endometrial carcinoma were included in the study. Women with documented premature primary or secondary ovarian failure were be excluded.

Exposure variables

Age at presentation; Parity; Body mass index; Hypertension; Diabetes mellitus; Hormone therapy including tamoxifen; Personal history of another cancer; Family history of cancer.

Outcome variables

Histological type; Grade; Stage; Type of surgery; Myometrial depth involvement; Lymph node spread; Extrauterine spread other than lymph node; Adjuvant treatment.

Sample Size

15 patients aged less than 55 years were obtained during the study period. They were matched with 30 randomly selected endometrial cancer patients aged more than 55 years.

Data collection

All the endometrial cancer case files for the 5-year period 2014 – 2018 were retrieved from the gynaecologic oncology department records. Patients meeting the inclusion criteria were selected and the above variables as documented in the case files were manually recorded in the data collection sheet over a 2-month period.

These data were entered in EXEL using EPIDATA and thereafter exported to STATA for analysis.

Data Analysis

Data were analysed using descriptive statistics. Frequency and percentages were used to describe discrete variables and the median and range for continuous variables. Chi-squared and Fisher's exact test were used. Statistical significance was defined as $P < 0.05$

Ethical Considerations

Ethics approval was sought from the research and ethics committee of Stellenbosch University and Tygerberg Hospital before carrying out the study. The Ethics Reference Number is S19/10/249

Patients' confidentiality was preserved. Data was anonymised and the data was kept in a password-protected file. A waiver of consent was granted because only retrospective data were used.

RESULTS

Overall, 45 patients that met the inclusion criteria were selected. Only 15 patients (median age 52) aged 55 or less were found during the 5-year study period. 30 patients (median age 66.5 years) aged more than 55 years were randomly selected for comparison between the two age groups.

The data collected are shown in the tables 2 and 3 below.

Table 2

Exposure characteristics

Characteristics	<55 years of age	>55 years of age
	n=15 (%)	n=30 (%)
Parity		
Parous	12 (80%)	21 (70%)
Nulliparous	3 (20%)	9 (30%)
BMI		
30-39.9	8 (53.3%)	17 (56.7%)
>40	7 (46.7%)	13 (43.3%)
Hypertension		
Yes	10 (66.7%)	21 (70%)
No	5 (33.3%)	9 (30%)
Diabetes Mellitus		
Yes	7 (46.7%)	8 (26.7%)
No	8 (53.3%)	22 (73.3%)
Hormone therapy (including tamoxifen)		
Yes	0 (0%)	2 (6.7%)
No	15 (100%)	28 (93.3%)
Personal history of another cancer		
Yes	2 (13.3%)	3 (10%)
No	13 (86.6%)	27 (90%)
Family history of Cancer		
Yes	4 (26.7%)	6 (20%)
No	11 (73.3%)	24 (80%)

BMI: Body Mass Index kg/m^2

Table 3

Outcome characteristics

Characteristics	<55 years of age	>55 years of age
	n=15 (%)	n=30 (%)
Histological Type		
Type 1	15 (100%)	15 (50%)
Type 2	0 (0%)	15 (50%)
Histological Grade		
Low grade (1 & 2)	13 (86.7%)	17 (56.7%)
High grade (3)	2 (13.3%)	13 (43.3%)
Surgery Type		
TAH+BSO+PLND	8 (53.3%)	8 (26.7%)
TAH + BSO + Omental biopsy	3 (20%)	2 (6.7%)
TAH + BSO	4 (26.7%)	9 (30%)
TAH + BSO + PLND + Omentectomy	0 (0%)	7 (23.3%)
TAH + BSO + Omentectomy	0 (0%)	3 (10%)
TAH + BSO + PLND + Omental Biopsy	0 (0%)	1 (3.3%)
Myometrial Depth Involvement		
Inner half	11 (73.3%)	11 (36.7%)
Outer half	4 (26.7%)	19 (63.3%)
Lympho-vascular Space Invasion		
Yes	3 (20%)	12 (40%)
No	12 (80%)	18 (60%)
Lymph Node Spread		
Yes	2 (13.3%)	5 (16.7%)
No	6 (40%)	11 (36.7%)
Not done	7 (46.7%)	14 (46.6%)
Extrauterine Spread other than Lymph Nodes		
Yes	3 (20%)	19 (63.3%)
No	12 (80%)	11 (36.7%)

Table 3 *(continued)*

Characteristics	<55-years-old	>55-years-old
	n=15 (%)	n=30 (%)
Stage		
1	11 (73.4%)	10 (33.3%)
2	2 (13.3%)	8 (26.7%)
3	2 (13.3%)	9 (30.0%)
4	0 (0%)	3 (10.0%)
Adjuvant Treatment		
Yes	6 (40%)	24 (80%)
No	9 (60%)	6 (20%)

TAH: Total Abdominal Hysterectomy, BSO: Bilateral Salpingo-oophorectomy, PLND: Pelvic Lymph Node Dissection

Parity

Only 3 patients (20%) in the <55-year-old cohort and 9 patients (30%) in the >55-year-old group were nulliparous.

Body mass index

All the study participants were found to have a least class 2 obesity with a body mass index (BMI) > 30 kg/m^2. A particularly high prevalence of class 3 (morbid) obesity with a BMI > 40 kg/m^2 was noted in both groups, 7 patients (46.7%) in the <55-year-old cohort and 13 patients (43.3%) in the >55-year-old group respectively.

Hypertension

10 patients (66.7%) in the <55-year-old cohort were found to be hypertensive as compared to 21 patients (70%) in >55-year-old group.

Diabetes Mellitus

7 patients (46.7%) in the <55-year-old cohort had diabetes mellitus as compared to only 8 patients (26.7%) in the >55-year-old group.

Hormone therapy

None of the study participants had hormone replacement therapy, and only 2 patients in the >55-year-old group had tamoxifen for breast cancer.

Personal history of previous cancer

Only a small number of participants reported a history of previous cancer in the study. In the <55-year-old cohort, 2 patients had a history of colon cancer. Lynch syndrome was eventually excluded in both patients. In the >55-year-old group, 2 patients had a history of breast cancer and were treated with tamoxifen; and 1 patient had a history of thyroid cancer and thigh leiomyosarcoma.

Family history of cancer

4 patients (26.7%) in the <55-year-old cohort had a family history of cancer as compared to 6 patients (20%) in the >55-year-old group.

Tumour Type

All of the patients in the <55-year-old group had endometrioid adenocarcinoma as compared to 15 patients (50%) in the >55-year-old group.

Tumour grade

In the >55-year-old group, 17 patients (56.7%) had low-grade tumour and 13 patients (43.3%) had high grade tumour respectively. In contrast, low-grade tumour prevalence in the <55-year-old cohort was 86.7% (13 patients) as compared to high-grade tumour, 13.3% (2 patients).

Surgical management

All the patients in the study were offered surgical management with a staging laparotomy consisting of total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO). Pelvic lymph node dissection (PLND) was carried out based on the histological type and grade, myometrial depth invasion, and intra-operative findings. Omental biopsy or omentectomy was done based on intraoperative findings only.

- 4 patients (26.7%) in the <55-year-old group had only TAH+BSO as compared to 9 patients (30%) in the >55-year-old group.
- Interestingly, similar rates of PLND were noted in both groups. 8 patients (53.3%) in the <55-year-old group had PLND as compared to 16 patients (53.3%) in the >55-year-old group.
- 3 patients (20%) had an omental biopsy in the <55-year-old group as compared to 3 patients (10%) in the >55-year-old group.
- None of the patients in the <55-year-old group had an omentectomy as compared to 10 patients (33.3%) in the >55-year-old group.

Myometrial depth involvement

In the <55-year-old cohort, myometrial depth involvement of the inner-half and outer-half was found in 11 patients (73.3%) and 4 patients (26.7%) respectively. Whereas in the >55-year-old group, 11 patients (36.7%) with inner-half and 19 patients (63.3%) with outer-half myometrial depth involvement was seen.

Lympho-vascular space invasion

Lympho-vascular space invasion was found in 3 patients (20%) in the <55-year-old cohort as compared to 12 patients (40%) in the >55-year-old group.

Lymph node spread

For those who underwent pelvic lymph node dissection, 2 patients (13.3%) were found to have positive lymph nodes in the <55-year-old group as compared to 5 patients (16.7%) in the >55-year-old group.

Extrauterine spread other than lymph nodes

Extrauterine metastasis of the tumour was found in 3 patients (20%) in the <55-year-old group as compared to 19 patients (63.3%) in the >55-year-old group.

Stage

In the <55-year-old group, 11 patients (73.4%) had Stage 1 disease, 2 patients (13.3%) had Stage 2, 2 patients (13.3%) had Stage 3, and none had Stage 4 disease. In the >55-year-old cohort, 11 patients (33.3%) had Stage 1, 8 patients (26.7%) had Stage 2, 9 patients (30%) had Stage 3, and 3 patients (10%) had Stage 4 disease.

Adjuvant therapy

6 patients (40%) in the <55-year-old group required adjuvant therapy as compared to 24 patients (80%) in the >55-year-old group.

Statistical analysis was performed using the chi-squared test, Fisher exact test, and p-values for the outcome variables are shown in Table 4 below.

Table 4

Association between endometrial cancer and outcome characteristics between patients aged <55 years and >55 years of age.

Characteristics	<55 years of age	>55 years of age	p-value
	n=15 (%)	n=30 (%)	
Grade			**0.044**
Low grade (1 & 2)	13 (86.7%)	17 (56.7%)	
High grade (3)	2 (13.3%)	13 (43.3%)	
Myometrial Depth Involvement			**0.02**
Inner	11 (73.3%)	11 (36.7%)	
Outer	4 (26.7%)	19 (63.3%)	
Lympho-vascular Space Invasion			0.18
Yes	3 (20%)	12 (40%)	
No	12 (80%)	18 (60%)	
Lymph Node Spread			0.95
Yes	2 (13.3%)	5 (16.7%)	
No	6 (40%)	11 (36.7%)	
Not done	7 (46.7%)	14 (46.6%)	
Extrauterine Spread other than Lymph Node			**0.006**
Yes	3 (20%)	19 (63.3%)	
No	12 (80%)	11 (36.7%)	
Stage			**0.107**
1	11 (73.4%)	10 (33.3%)	
2	2 (13.3%)	8 (26.7%)	
3	2 (13.3%)	9 (30.0%)	
4	0 (0%)	3 (10.0%)	
Adjuvant Treatment			**0.007**
Yes	6 (40%)	24 (80%)	
No	9 (60%)	6 (20%)	

Highlighted bold values indicate statistical significance at $P < 0.05$

Comparison of outcomes between the <55-year-old and <55-year-old group showed statistical significance at a p-value < 0.05 for the grade of tumour (p-value 0.004), myometrial depth invasion (p-value 0.02), extrauterine spread other than lymph nodes (p-value 0.06) and adjuvant therapy (p-value 0.007). No association was found for lympho-vascular invasion, lymph node spread and stage between the two groups.

DISCUSSION

This is the first study investigating the association of age and characteristics of endometrial carcinoma in young patients in South Africa.

In our study, the number of nulliparous women was low, 3 patients (20%) in the <55-year-old group and 9 patients (30%) in the >55-year-old cohort. Therefore, a correlation between parity and endometrial cancer could not be inferred. However previous studies have shown that gravidity and parity have a strong inverse relationship with endometrial cancer. [63] More recently, Husby et al. explored the association between pregnancy duration and the risk of endometrial cancer using a nationwide register looking at all Danish women born from 1935 to 2002. [64] They found that a first pregnancy was associated with a significantly reduced risk of endometrial cancer, whether it was ended with an induced abortion (aRR 0.53; 95% CI 0.45-0.64) or childbirth (aRR 0.66; 95% CI 0.61-0.72), and each subsequent pregnancy was associated with an additional reduction in risk, irrespective of induced abortion (aRR 0.81; 95%CI 0.77-0.86) or childbirth (aRR 0.86; 95%CI 0.84-0.89).

Our findings were deeply concerning in regard to obesity. All of the participants were obese, with 46.7% in the <55-year-old cohort and 43.3% in the >55-year-old group having Class III obesity. Patients with obesity have higher levels of endogenous oestrogen due to the peripheral conversion of conversion of androstenedione to oestrone and aromatisation of androgens to oestradiol in the adipose tissue, hence are at increased risk for developing endometrial hyperplasia and endometrial cancer. Setiawan et al. did a pooled analysis of from 10 cohort and 14 case-controlled studies with over 14,000 endometrial cancer patients and over 35,000 controls. [65] They found out that the odds ratio (OR) for Type I endometrial cancer were OR 1.5 for overweight, OR 2.5 for Class I obesity, OR 4.5 Class II obesity, and OR 7.1 for Class III obesity. For Type II endometrial cancer the ORs were 1.2 for overweight, 1.7 for Class I obesity, 2.2 for

Class II obesity, 3.1 for class III obesity. Moreover, in a prospective cohort study Calle et al. reported that women with Class III obesity have a 62% higher death rate from all cancers combined than women of normal weight. [66] Lifestyle modifications such as healthy eating and exercise are key preventive measures. The Government of South Africa has implemented several strategies to fight continuing obesity epidemic such as awareness campaigns to promote healthy eating and regular exercise, building of sports facilities and wellness parks and introducing a sugar tax. Bariatric surgery also has a role and has been shown to decrease the prevalence of endometrial cancer by 60 to 80%. [67]

In our cohort, the prevalence of hypertension was similar in both groups, and a significant number of patients in the <55-year-old group had diabetes mellitus as compared to the >55-year-old group (46.7% vs 26.7%). However, hypertension and diabetes mellitus have not been conclusively shown to risk factors of endometrial cancer as obesity is often a confounding factor that accounts for the increased risk. Indeed, in our study obesity seems to be the most likely cause of the increased risk of endometrial cancer.

In our study, none of the participants who were menopausal had hormone replacement therapy. However, the current consensus is that menopausal hormone replacement therapy with combined oestrogen and progestin does not confer an increased risk for endometrial hyperplasia. [68]

2 of our study participants in the >55-year-old-group had a history of breast cancer and tamoxifen use. Tamoxifen is a selective oestrogen receptor modulator with both agonist and antagonist properties depending on the site of action and level of circulating oestrogen. In postmenopausal women it has a partial agonist action on the endometrium whereas in premenopausal women it exerts an antagonist effect on the endometrium. Tamoxifen use is linked with a two- to three- fold increased risk endometrial cancer in postmenopausal women. [69] However, an increased risk of endometrial cancer in premenopausal women on tamoxifen has not been demonstrated till now.

There is evidence that the levonorgestrel intrauterine system reduces the incidence of endometrial hyperplasia in women on tamoxifen. [70] However, many breast cancer patients are progesterone receptor positive and there is the concern that adding a progestogen might increase the risk of breast cancer recurrence. Therefore, its use is not routinely recommended. Hence, a high degree of suspicion should be excised for any abnormal uterine bleeding in women on tamoxifen therapy.

In our study 2 participants in the <55-year-old group had a personal history of colon cancer. Lynch syndrome is an autosomal dominant caused by one of several genetic mutations that impair DNA mismatch repair. Patients with Lynch syndrome have an increased risk of developing endometrial cancer and ovarian cancer at an earlier age than the general population. [14] For endometrial cancer the mean age at diagnosis is 46 to 54 years old as compared to a mean age of 61 years old in other women. Thus, women should be counselled about the increased risk of endometrial and ovarian cancer and to seek medical prompt medical attention for any abnormal uterine bleeding or any of the non-specific symptoms of ovarian cancer. Surveillance in asymptomatic women is warranted with annual endometrial biopsy starting from age 30. However, surveillance for ovarian cancer has not been shown to increase survival and is associated with a high false-positive rate. Risk reducing total hysterectomy and bilateral salpingo-oophorectomy is offered once the woman has completed childbearing. Our 2 patients underwent microsatellite instability testing and Lynch syndrome was excluded.

In a meta-analysis of 16 studies to assess the risk of endometrial cancer associated with a first-degree family history of endometrial cancer, Win et al. found the relative risk to be 1.82 (CI 1.65-1.98). [71] However, till now no candidate genes have been identified consistently. In our study, there was no strong association between family history and the occurrence of endometrial cancer.

All the women in our study were surgically staged with a total abdominal hysterectomy and bilateral salpingo-oophorectomy. Pelvic lymph node dissection was done based on histological type, grade, myometrial depth invasion, and intraoperative findings.

Nowadays there is a trend towards minimally invasive surgery such as total laparoscopic hysterectomy (TLH) for early-stage endometrial cancer. It is well established that minimally invasive procedures result in less post-operative complications, shorter hospital stay duration, and better quality of life than conventional laparotomy. Moreover, the LAP2 and LACE trials showed similar 5-year survival rates for women with Stage I disease who had either staging laparotomy or laparoscopy. [72] [73] Galaal et al. conducted a meta-analysis of eight randomized controlled trials comparing laparoscopy with laparotomy for the surgical management of early-stage endometrial cancer. They found no significant difference in the risk of death or disease recurrence between the two groups. [74]

However, careful patient selection must be done in choosing a surgical modality. Indeed, the LAP2 trial showed a high conversion rate (25.8%) from laparoscopy to laparotomy and was strongly correlated with BMI. [72] In our study all our participants were obese with 46.7% in the <55-year-old cohort and 43.3% in the >55-year-old group having Class III obesity. This justifies the choice of opting for a laparotomy in our population.

Pelvic lymph node dissection is an area of active controversy. With a significantly increased risk of morbidity, the role of PLND in the absence of clinical evidence of metastatic disease and low-risk endometrial cancer has been investigated. Indeed, both Beneditti Panici et al. and the ASTEC trial showed no difference in overall survival and recurrence-free survival for PLND in women with early-stage endometrial cancer. [59] [60] Selective lymphadenectomy and sentinel node evaluation has emerged as alternatives to complete PLND to guide adjuvant therapy and prognosis. In our study, 8 patients (53.3%) in the <55-year-old group had lymphadenectomy, among which 2 had positive lymph nodes. However, we found no statistical difference between the prevalence of positive lymph nodes between the <55-year-old and >55-year-old group (p-value 0.95).

In our study, none of the patients were offered conservative management. Based on our population demographics, and with patients often living very far from the hospital, the increased surveillance required for conservative treatment poses significant challenges. Moreover, most of our patients have completed their families and did not desire fertility-sparing treatment.

All the patients in the younger cohort (100%) had endometrioid carcinoma (Type 1) as compared to 50% in the >55-year-old group. Our study agrees with Burleigh et al. In their study for endometrial cancer patients less than 45 years of age, they found that patients in the High-Oestrogen group, which was defined as patients with obesity, polycystic ovarian syndrome, oestrogen producing tumours, as well as exogenous exposure to unopposed oestrogen therapy and tamoxifen, 95% (144 of 188 patients) had endometrioid pathology. [75]

In our study, 86.7% in the <55-year-old group had low grade tumour (grade 1 and 2) as compared to 43.3% in the >55-yeard old group. This is in agreement with a study by Pellerin et al. looking at the pathological characteristics of endometrial cancer in women less than 45 years of age. [76] Out of 38 patients, 20 (52.6%) had Grade 1, 10 (26.3%) had Grade 2, and 8 (21.1%) had grade 3 histology respectively. They

concluded that young patients with endometrial carcinoma tend to have higher degree of tumour differentiation and better prognosis at compared to women older than 45 years of age. Indeed, we found a statistical significance (p-value <0.044) between the younger and older aged groups.

We found that myometrial depth invasion was statistically significant between the two groups with a p-value 0.02. Indeed, in the <55-year-old group only 26.7% had more than half (outer) myometrial depth involvement as compared to the older group (63.3%). Both Soliman et al. and Tran et al. reported similar findings in their study of endometrial cancer in young women, 22% and 24% respectively. [77] [78]

Like the results of Tran et al., we found no statistical significance for lympho-vascular space invasion (p-value 0.18) and lymph node involvement (p-value 0.95) between the younger and older cohort. We found positive LVSI in 20% patients in the younger group as compared to Soliman et al. 31% and Tran et al. 10%. Furthermore, Guntapalli et al. showed that patients with LVSI positive tumours are an independent risk factor for nodal metastasis and have poor survival. [79]

We found similar lymph node involvement (13%) as compared to Soliman et al. (13%) and Tran et al. (17%) in the younger cohort. Furthermore, lymphadenectomy was not done for almost half of the young patient cohort in the studies.

However, despite favourable factors such as less aggressive histological type, low grade and less myometrial invasion in younger women with endometrial carcinoma, our study showed no statistical difference when compared to older patients for lymph node involvement. This is in contrast with the results of Vargas et al. who carried out a SEER analysis of tumour size, depth of invasion and histologic grade as prognostic factors for lymph node involvement in endometrial cancer. [80] They concluded that women with low-risk endometrial cancer, as defined by the Mayo criteria, have a low rate of lymph node metastasis.

Indeed, since patients with low-risk endometrioid carcinoma (grade 1 or 2 and superficial myometrial invasion <50%) have a low risk of lymph node involvement, and two randomized control trials (Benedetti Panici et al. and the ASTEC Trial) did not show a survival benefit, the ESMO-ESGO-ESTRO consensus conference on endometrial cancer recommends not performing lymphadenectomy in low-risk patients. [59] [60] [27]

There was significantly less extrauterine spread other than lymph nodes in the <55-year-old group as compared to the >55-year-old group with a p-value 0.006. Our results agree with numerous studies supporting the fact that younger women with endometrial cancer are associated with a lower incidence of distant metastasis.

A significantly higher proportion of patients, 73.3% in the <55-year-old group had Stage 1 disease as compared to 33.3% in the >55-year-old cohort. However, we found no statistical difference between the two groups they were compared across all stages (p-value 0.107). Even though our study is in agreement with Evan-Metcalf et al. who found no significant difference in the distribution for Stages I-IV between <45-year-old and older groups [81] several subsequent studies have not demonstrated such an association. Our results might be explained by a small sample size and the cut-off age value of 55 for the two groups.

Our study showed that significantly less patients in the younger age group required adjuvant therapy (40% vs 80%). We found a statistical significance (p-value <0.007) between the two groups. Decision to offer adjuvant radiotherapy was individualized based on the risk category for of the patient. Indeed, among the 6 patients (40%) in the younger-aged group who were offered radiotherapy, 4 were classified as high-risk and the remaining 2 as intermediate-high risk. This was based on tumour type, tumour grade, outer-half myometrial invasion, lympho-vascular space invasion, and cervical involvement. Patients with low-risk disease were not offered adjuvant radiotherapy as several trials (PORTEC-1, GOG#99 and ASTEC) have not demonstrated a survival benefit in that category. [82] [83] [60] Moreover, even though there was significant reduction in rates of vaginal or pelvic recurrence after external-beam radiotherapy (ERBT), the risks of complications associated with ERBT outweighs its benefit for locoregional control.

Our study is limited by its sample size and the cut-off age of 55 years for the two groups. However, our study was conducted at a large referral centre and reflects a representative sample of the population.

CONCLUSION

It is reassuring that the incidence of endometrial cancer in young patients was low in our study. However, obesity has emerged as a major risk factor, and it seems that endometrial cancer in our population is mainly driven by oestrogen excess. With the disproportionate prevalence of obesity in young women in South Africa, prevention measures are key strategies to reduce the incidence of endometrial cancer in this age group. Moreover, a high index of suspicion and a low threshold for endometrial sampling is warranted for high BMI patients presenting with persistent abnormal uterine bleeding. Our study agrees with others in terms of favourable tumour characteristics such as type, grade, myometrial depth invasion, extrauterine spread. Additionally, most of the patients in the younger cohort had no lympho-vascular space invasion and presented with Stage I disease. Despite those favourable characteristics, no significant difference for lymph node involvement was found between the two groups. This highlights a possible role for sentinel-node evaluation in our patient population. Moreover, with advances and more experience in laparoscopic surgery techniques, low-risk high-BMI patients can be staged with less morbidity and shorter-duration hospital stays than is typically associated with open laparotomy. Even though fertility-sparing treatment has been successful in selected women, providing conservative management to our patients has proved to be challenging due to the local population demographics. Furthermore, in our cohort of young patients, most have either completed their families or did not desire future fertility. Thus, at present, only a very limited number of women can be offered a conservative approach in the management of endometrial cancer.

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